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Sensitivity and specificity of using CD4+ measurement and clinical evaluation to determine antiretroviral treatment failure in Thailand

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Monitoring efficacy of antiretroviral therapy;
Risk factors of antiretroviral treatment failure

Summary
Objective: We conducted a study to evaluate the sensitivity and specificity of using CD4+ measurement and clinical evaluation to detect antiretroviral treatment failure in HIV-infected patients who had received their first regimen of highly active antiretroviral therapy (HAART). The secondary objective was to determine the prevalence and risk factors of virological failure.
Methods: A retrospective cohort study was conducted at Chiang Mai University Hospital, Thailand. Univariate analysis was performed to compare risk ratios between patients with and without virological failure. Sensitivity and specificity of the immunological and/or clinical criteria in comparison with virological criteria were calculated using 2 by 2 tables.
Results: From January 2003 to December 2005, 327 HIV-infected patients were enrolled. The median follow-up period was 19 months (range 6—42 months). Virological failure was detected in 9.2% of patients. Patients with a previous history of opportunistic infection had a greater risk for developing virological failure (OR = 2.66, 95% CI = 1.1—6.4). Using the combined immunological and clinical criteria to detect antiretroviral treatment failure, the sensitivity was 20.0% and the specificity was 85.9%.
Conclusions: Our study, which was limited by small numbers, was not able to demonstrate that immunological or clinical criteria can adequately replace virological criteria for the determination of treatment failure.

Introduction

The use of highly active antiretroviral therapy (HAART) is associated with a significant survival benefit and a dramatic reduction in the incidence of opportunistic infections in HIV-infected patients.[1—3] Currently, HAART has become a standard of care in the treatment of HIV infection in many parts of the world.

The outcome of antiretroviral therapy can be monitored using different methods including virological, immunological, and clinical evaluations.[4—7] Virological evaluation, i.e.,

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HIV RNA measurement, is generally accepted as the gold standard for monitoring of treatment outcome.[8–10] Using this method, early treatment failure can be detected and a change to other more effective antiretroviral regimens is then possible. However, in resource-limited settings, i.e., in most developing countries including Thailand, the cost of HAART is high and access to treatment may be relatively limited.[11,12] Adding to this the high cost of periodic viral measurements makes it almost impossible for all people in these developing countries to access antiretroviral therapy with effective monitoring. Therefore, two cheaper surrogate markers are routinely used to monitor the efficacy of therapy in the developing world, i.e., clinical assessment and CD4+ cell count. HIV RNA measurement is generally reserved for use in patients with immunological and/or clinical failure.[11,13]

In Thailand, the government provides free access to HAART for all HIV-infected patients who have indication(s) for use, following the national guidelines for HIV/AIDS management developed by the Ministry of Public Health.[13] These treatment guidelines are reviewed annually by panels of infectious disease and HIV/AIDS experts from throughout the country. Due to budget limitations, the national guidelines recommend performing CD4+ cell counts every 6 months, in addition to routine clinical evaluation, in all patients who receive HAART.[13] It also provides definitions of antiretroviral treatment failure using immunological and clinical criteria. HIV RNA measurement is recommended only in those patients who fulfill the immunological and/or clinical criteria for treatment failure.

This study was aimed at evaluating the sensitivity and specificity of using CD4+ measurement and clinical evaluation to detect antiretroviral treatment failure in the resource-limited setting. The secondary objective was to determine the prevalence and risk factors of virological failure in HIV-infected patients who had received their first regimen of HAART.

Methods

We conducted a retrospective cohort study in HIV-infected patients who were treated and followed up at the infectious disease outpatient clinic, Chiang Mai University Hospital from January 2003 to December 2005. All the subjects had documented HIV infection and met the following criteria: (1) $\geq$15 years of age; (2) had received their first regimen of HAART following the national guidelines for HIV/AIDS management; (3) CD4+ cell count had been carried out every 6 months after initiation of HAART; and (4) HIV RNA measurement had been carried out at 6 months or later after initiation of HAART.

Definitions of terms

We used the definitions of antiretroviral treatment failure following the national guidelines for HIV/AIDS management developed by the Thai Ministry of Public Health.[13]

Immunological failure: the absence of increase or a decrease in the CD4+ cell count of more than 30% from the highest value after at least 6 months of HAART.

Clinical failure: the development of an AIDS-associated condition or death after at least 6 months of HAART.

Virological failure: an HIV RNA measurement of more than 50 copies/ml after at least 6 months of HAART.

Data collection

We recorded the following data: (1) demographic characteristics at the initiation of HAART; (2) CD4+ cell counts at months 0, 6, 12, and 18 of HAART; and (3) HIV RNA measurements after initiation of HAART.

Statistical analysis

The virological, immunological, and clinical failure prevalences are expressed in percentage terms. Demographic data, medical history, laboratory data, and therapeutic outcome are expressed in terms of percentage, mean $\pm$ stanstandard deviation (SD), and range.

Univariate analysis of demographic and laboratory data of patients with and without virological failure was performed to compare risk ratios between groups. Categorical data were assessed by the Chi-square test or Fisher's exact test as appropriate. Continuous data were assessed by the Student's *t*-test or Mann–Whitney U-test as appropriate. A two-sided test was used to indicate statistical significance at a p value of <0.05.

Sensitivity, specificity, positive predictive value, and negative predictive value of the immunological and/or clinical criteria in comparison with virological criteria were calculated using 2 by 2 tables.

SPSS software version 13.0 (SPSS for windows, Rel. 13.0.1997; Chicago, USA, SPSS Inc.) was used for all statistical analyses.

Results

Demographic data

During the three-year period from January 2003 to December 2005, 327 HIV-infected patients were enrolled in the study. For the regimen of HAART, 279 patients (85.3%) received a fixed-dose combination of stavudine, lamivudine, and nevirapine (GPO-VIR®, manufactured by the Thai Government Pharmaceutical Organization), 16 (4.9%) received a regimen containing efavirenz plus two nucleoside reverse transcriptase inhibitors (NRTI), and 32 (9.8%) received a regimen containing nevirapine plus two NRTIs. There were 140 men (42.8%) and 187 women (57.2%) with a mean age of 37.8 $\pm$ 7.8 years (range 21–65 years). One hundred and eighty-seven patients (57.2%) had had previous opportunistic infections before initiation of HAART; these included pneumocystis pneumonia (43 patients, 13.1%), penicilliosis marneffei (32 patients, 9.8%), pulmonary tuberculosis (26 patients, 8.0%), cryptococcosis (18 patients, 5.5%), and cytomegalovirus retinitis (12 patients, 3.7%).

The mean CD4+ T cell counts at baseline, 6 months, and 12 months after initiation of HAART were 108.0 $\pm$ 117.4, 219.0 $\pm$ 146.3, and 273.5 $\pm$ 160.0 cells/mm^3, respectively.

Prevalence and risk factors of antiretroviral treatment failure

Among 327 eligible patients, 14 (4.3%), 35 (10.7%), and 16 (4.9%) met the criteria of virological failure, immunological

Table 1 Demographic characteristics, medical history, and laboratory data of patients with and without virological failure

Characteristics	Patients with virological failure ($N = 30$)	Patients without virological failure ($N = 297$)	p Value
Age, years (mean ± SD)	36.7 ± 7.5	38.0 ± 7.8	0.38
Sex male (%)	17 (56.7)	123 (41.41)	0.12
Previous history of opportunistic infection (%)	23 (76.7)	164 (55.2)	0.03
Baseline CD4+ cell count before initiation of HAART (mean ± SD)	93.3 ± 125.11	109.5 ± 116.7	0.50

HAART, highly active antiretroviral therapy.

failure, and clinical failure, respectively. The median follow-up period was 19 months (range 6—42 months). The comparison of demographic characteristics, medical history, and laboratory data between the groups of patients with and without virological failure are shown in Table 1. The univariate analysis revealed only one risk factor for developing virological failure, i.e., previous history of opportunistic infection (OR = 2.66, 95% CI = 1.1—6.4).

Sensitivity and specificity of immunological and clinical criteria

In this study, virological measurement of more than 50 copies/ml was used as the gold standard to evaluate antiretroviral treatment failure. The correlations between number of patients with and without virological failure versus immunological failure, virological failure versus clinical failure, and virological failure versus immunological and/or clinical failure were performed using 2 by 2 tables (data not shown here). Sensitivity, specificity, positive predictive value, and positive predictive value of using immunological and clinical criteria to determine antiretroviral treatment failure were calculated and are shown in Table 2. Sensitivity, specificity, positive predictive value, and positive predictive value of using combined immunological and clinical criteria to determine virological failure at different cut-offs are shown in Table 3.

Discussion

Due to significant reductions in cost and the wide availability of generic antiretroviral drugs, antiretroviral therapy is currently affordable even in some developing countries. In Thailand, the national policy is that all HIV-infected patients in the country can have access to antiretroviral treatment.[14] In this study, we have shown the efficacy of three antiretroviral treatment regimens commonly used in Thailand; the fixed-dose combination of generic antiretroviral drugs (GPO-VIR®) manufactured by the Thai Government Pharmaceutical Organization is the most common regimen, being used in 85% of patients.

Virological failure in our study was 9.2% after a median follow-up duration of 19 months. This result is in the range of failure rates found in a previous study by Anekthananon et al. from Bangkok, Thailand (2.4% by on-treatment and 19.8% by intention-to-treat analysis).[15] In addition, our study showed that a previous history of opportunistic infection was the only risk factor for virological failure. However, this was a retrospective study that was not designed to adequately collect the data on adherence to antiretroviral therapy. A prospective study may be more appropriate to determine the relative risk of developing treatment failure in these patients.

In Thailand, the national guidelines for HIV/AIDS management recommend using clinical and immunological criteria to monitor the outcome of antiretroviral treatment.[13]

Table 2 Sensitivity, specificity, positive predictive value, and positive predictive value of using immunological and clinical criteria to determine antiretroviral treatment failure

	Immunological criteria	Clinical criteria	Combined immunological and clinical criteria
Sensitivity (%)	13.3	10.0	20.0
Specificity (%)	89.6	95.6	85.9
Positive predictive value (%)	8.6	25.0	12.5
Negative predictive value (%)	90.8	91.6	91.4

Table 3 Sensitivity, specificity, positive predictive value, and positive predictive value of using combined immunological and clinical criteria to determine virological failure at different cut-offs

	Viral load >50 copies/ml	Viral load >500 copies/ml	Viral load >1000 copies/ml	Viral load >5000 copies/ml
Sensitivity (%)	20.0	13.3	14.3	18.2
Specificity (%)	85.9	85.3	85.3	85.4
Positive predictive value (%)	12.5	4.2	4.2	4.2
Negative predictive value (%)	91.4	95.3	95.7	96.6

This strategy is generally used in the many countries where healthcare resources are limited.[11] Our study showed that antiretroviral treatment failure was suspected in 10.7% and 4.9% of patients using immunological criteria and clinical criteria, respectively. With the use of HIV RNA measurement as the gold standard, the sensitivities of using either immunological or clinical criteria to determine antiretroviral treatment failure were found to be extremely low (13.3% and 10.0%, respectively). However, the specificities of using these two markers were found to be acceptably high (89.6% and 95.6%, respectively). Although the 20.0% sensitivity using the combined clinical and immunological criteria to detect antiretroviral treatment failure is slightly higher than the sensitivity using one marker alone, we would miss 80% of patients who have treatment failure using virological criteria. Using various virological cut-offs does not improve the sensitivity and predictive values (Table 3). These patients, in particular those with a viral load >1000 copies/ml, need genotypic resistance testing and proper antiretroviral substitution, but treatment would be left unchanged. If they continued on a failing antiretroviral regimen, it is possible that the resistance mutation genes would accumulate and cross resistance to all antiretroviral drugs in the same classes would ultimately develop.[16] In the presence of extensive resistance mutations, change to other effective antiretroviral regimens is unlikely to work, and the cost of salvage therapy is relatively high.[17] Our study therefore suggests that it is not appropriate to use only the clinical and immunological criteria to monitor the outcome of antiretroviral therapy. HIV RNA measurement is more sensitive and could detect early antiretroviral treatment failure in patients who may not have clinical and immunological failures. A prospective study to assess the cost-effectiveness of using HIV RNA as a monitoring tool is necessary.

In conclusion, monitoring the outcome of antiretroviral therapy using immunological and clinical criteria had a low sensitivity to detect treatment failure. Our study, which was limited by small numbers, was not able to demonstrate that immunological or clinical criteria can adequately replace virological criteria for treatment failure.

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Conflict of interest: No conflict of interest to declare.

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